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AGENSYS C/O MORRISON & FOERSTER LLP
3811 VALLEY CENTRE DRIVE, SUITE 500
SAN DIEGO, CA 92130

EXAMINER	
BUNNER, BRIDGET E	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 10/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/024,652	CHALLITA-EID ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-7,9-13,15;70 and 78-88* is/are pending in the application.

4a) Of the above claim(s) *15,70 and 84-88* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-7,9-13 and 78-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *4-7,9-13,15,70 and 78-88* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 June 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/14/04; 2/12/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendments 28 June 2002, 22 April 2004, and 19 July 2004 have been entered in full. Claims 4-7, 9-15, 65-70, 75-77, 81, and 86 are amended. Claims 1-3, 8, 14, 16-64, 71-74 are cancelled. Claims 78-88 are added.

Election/Restrictions

Applicant's election without traverse of Group I, claims 4-7, 9-13, and 78-83, drawn to an antibody that specifically binds a protein, in the reply filed on 19 July 2004 is acknowledged.

Claims 15, 70, and 84-88 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 19 July 2004.

Claims 4-7, 9-13, and 78-83 are under consideration in the instant application.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). **Specifically, the sequences disclosed in Figures 1, 2A-2C, 3A-3B, 4A-4B, 18, and 25 are not accompanied by the required reference to the relevant sequence identifiers.** This application fails to comply with the requirements of 37 CFR 1.821 through 1.825. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825).

Specification

1. The disclosure is objected to because of the following informalities:

2. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. (It is noted that numerous hyperlinks are disclosed throughout the specification, including the Tables.) Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

3. The Brief Description of Drawings does not refer to Figure 4B or Figures 25A-25C.

4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "ANTIBODY THAT BINDS ZINC TRANSPORTER PROTEIN 108P5H8".

Appropriate correction is required.

Claim Objections

5. Claims 4, 11, and 12 objected to because of the following informalities:

6. Claims 4, 11, and 12 recite a "." after the term "SEQ ID NO". This issue could be overcome by removing the "." in this part of the claim.

Appropriate correction is required.

Claim Rejections - 35 USC § 101 and 35 § USC 112, first paragraph

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 4 and 9 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter. The claims read on a product of nature in that the claimed antibody is not "isolated". For example, the claims encompass polyclonal sera that has not been removed from the human or animal. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See *Diamond v. Chakrabarty,* 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "isolated" or "purified" as taught by page 84, lines 33-38 through pg 88, lines 1-8 of the specification. See MPEP 2105.

8. Claims 4-7, 9-13, and 78-83 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility. Novel biological molecules lack well established utility and must undergo extensive experimentation.

Specifically, claims 4-7, 9-13, and 78-83 are directed to an antibody or fragment thereof that specifically binds to a protein having at least 90% sequence identity to SEQ ID NO: 2570. The claims also recite that the antibody is a monoclonal antibody and that the monoclonal antibody is recombinantly produced. The claims recite that the antibody or fragment thereof may be labeled with a detectable marker or an agent. The claims recite a non-human transgenic animal that produces an antibody that specifically binds to a protein having at least 90% homology to SEQ ID NO: 2570. The claims recite a hybridoma that produces an antibody that specifically binds to a protein having at least 90% homology to SEQ ID NO: 2570. However, the instant specification does not teach any significance or functional characteristics of the 108P5H8 polypeptide (SEQ ID NO: 2570) or antibody. The specification only discloses that the

108P5H8 protein is normally expressed in a restricted set of tissues, but which is also expressed in prostate and other cancers (pg 46, lines 10-11, for example). The specification also does not disclose any specific methods or working examples for the production of the antibody or labeling of the antibody. Since the utility is not presented in mature form and significant further research is required, the utility is not substantial. The specification asserts the following as patentable utilities for the claimed putative antibody against 108P5H8 (SEQ ID NO: 2570):

1) to purify a 108P5H8-related protein or 108P5H8 homologues and related molecules (pg 33, lines 5-11)

2) to detect and quantify the presence of an 108P5H8 protein in a tissue or other biological sample (pg 32, lines 29-34; pg 38, lines 19-26)

3) to diagnose or treat 108P5H8-expressing cancers (pg 32, lines 23-28; pg 48, lines 10-32; pg 50-53; pg 65, lines 25-29; pg 66, lines, lines 11-17)

4) to bind 108P5H8 and inhibit its function (pg 68, lines 20-37 through pg 69, lines 1-16)

Each of these shall be addressed below.

1) to purify a 108P5H8-related protein or 108P5H8 homologues and related molecules. This asserted utility is not specific or substantial. Such assays can be performed with any antibody. Further, the specification discloses nothing specific or substantial for the 108P5H8 polypeptide of SEQ ID NO: 2570 purified by this method. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

2) to detect and quantify the presence of a 108P5H8 protein in a tissue or other biological sample. This asserted utility is not specific or substantial. Such assays can be performed with any antibody. Further, the specification discloses nothing specific or substantial for the 108P5H8 polypeptide detected by this method. The protein is not specific to one tissue

and is not associated with any disease or disorder. Also, evidence of mere expression in a tissue is not tantamount to a showing of a functional role of the 108P5H8 polypeptide. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

3) to diagnose or treat 108P5H8-expressing cancers. This asserted utility is not specific or substantial. Such assays can be performed with any antibody. The specification discloses nothing about the normal level of expression (if any) of the 108P5H8 polypeptide. The protein is not specific to one tissue and is present in normal and cancer tissues/cells (Figure 11). The specification does not disclose which specific cancers are associated with altered levels or forms of the 108P5H8 polypeptide. Significant further experimentation would be required of the skilled artisan to identify individuals with such a disease. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

4) to bind 108P5H8 and inhibit its function. This asserted utility is not specific or substantial. The specification discloses nothing specific or substantial for the 108P5H8 polypeptide of SEQ ID NO: 2570. Significant further experimentation would be required of the skilled artisan to identify the function of 108P5H8. Antibodies can be made to any polypeptide. However, if the specification discloses nothing specific and substantial about the polypeptide, therefore both polypeptide and its antibodies have no patentable utility. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

9. Claims 4-7, 9-13, and 78-83 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

9a. However, even if the claimed invention is eventually deemed to have a credible, specific and substantial asserted utility or a well established utility, the claims would remain rejected under 35 U.S.C. § 112, first paragraph. Specifically, the specification of the instant application teaches that embodiments of 108P5H8 proteins comprise variant, homolog, or analog polypeptides that have alterations in the amino acid sequence of 108P5H8 (pg 24, lines 31-34). The specification also discloses that embodiments of the invention include a wide variety of art-accepted variants or analogs of 108P5H8 proteins, such as polypeptides having amino acid insertions, deletions, and substitutions (pg 25, lines 22-24). However, the specification of the instant application does not teach a protein having at least 90% sequence identity to SEQ ID NO: 2570. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no

substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

Furthermore, structurally similar proteins may have different functions and one skilled in the art cannot rely upon structural similarity alone to determine functionality. For example, the undisclosed polypeptide variants that are 90% similar to the amino acid sequence of SEQ ID NO: 2570 may have different conformations and/or functions as compared to the disclosed

polypeptide comprising the amino acid sequence of SEQ ID NO: 2570. The altered conformations and/or functions of the undisclosed variants of 108P5H8 may prevent the antibodies of the instant claims from binding. Daniel et al. (Virology 202: 540-549, 1994) also discloses that primary amino acid sequences do not predict antigenic determinants and therefore, changing the amino acid sequence of a polypeptide may also affect antigenicity (pg 540, 547).

Additionally, the specification of the instant application discloses that nucleic acids that encode a 108P5H8 protein can be used to generate either transgenic animals or "knock out" animals that, in turn, are useful in the development and screening of therapeutically useful reagents (the bottom of pg 36 through pg 37). The specification teaches that embryonic stem cells or other types of embryonal cells can be transfected *in vitro* with a DNA vector capable of homologously recombining into the genome, injected into a blastocyst, and implanted into a pseudopregnant female animal resulting in progeny with transgenic DNA inserted into one or more copies of the targeted gene of interest. However, there are no methods or working examples disclosed in the instant application whereby a multicellular animal with the incorporated 108P5H8 gene is demonstrated to express the 108P5H8 peptide. There are also no methods or working examples in the specification indicating that a multicellular animal has the 108P5H8 "knocked out". The unpredictability of the art is *very high* with regards to making transgenic animals. For example, Wang et al. (Nuc. Acids Res. 27: 4609-4618, 1999; pg 4617) surveyed gene expression in transgenic animals and found in each experimental animal with a single "knock-in" gene, multiple changes in genes and protein products, often many of which were unrelated to the original gene. Likewise, Kaufman et al (Blood 94: 3178-3184, 1999) found transgene expression levels in their transfected animals varied from "full" (9 %) to

"intermediate" to "none" due to factors such as "vector poisoning" and spontaneous structural rearrangements (pg 3180, col 1, 2nd full paragraph; pg 3182-3183). Additionally, the specification does not provide guidance for identifying and isolating embryonic stem cells from species other than mouse, or for identifying other embryonal cells which are capable of contributing to the germline of any animal. At the time of filing, Campbell et al. teaches that, "in species other than the mouse the isolation of ES cells has proved more difficult. There are reports of ES-like cell lines in a number of species...However, as yet there are not reports of any cell lines which contribute to the germ line in any species other than mouse" (Campbell et al. Theriology 47(1): 63-72; see pg 65, 2nd paragraph). Thus, based on the art recognized unpredictability of isolating and using embryonic stem cells or other embryonal cells from animals other than mice to produce transgenic animals, and in view of the lack of guidance provided by the specification for identifying and isolating embryonal cells which can contribute to the germ line of any non-human mammal other than the mouse, such as dogs or cows, the skilled artisan would not have had a reasonable expectation of success in generating any and all non-human transgenic animals using ES cell technology.

Due to the large quantity of experimentation necessary to generate the infinite number of amino acid derivatives recited in the claims and to generate a transgenic animal expressing the 108P5H8 protein, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, the unpredictability of the effects of protein alterations on antibody binding, and the unpredictability of making transgenic animals, and the

breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

10. Claims 78-83 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to an antibody or fragment thereof that specifically binds to a protein having 90% sequence identity to SEQ ID NO: 2570, wherein the antibody or fragment is labeled with an agent. The claims recite that the agent is a diagnostic agent or a cytotoxic agent. Furthermore, the claims recite that the cytotoxic agent is selected from the group consisting of radioactive isotopes, chemotherapeutic agents, and toxins.

The specification of the instant application teaches that a "cytotoxic agent" refers to "a substance that inhibits or prevents the expression activity of cells, functions of cells and/or causes destruction of cells. The term is intended to include radioactive isotopes, chemotherapeutic agents, and toxins such as small molecule toxins or enzymatically active toxins of bacterial, fungal, plant or animal origin" (pg 13, lines 9-20; see also pg 50, lines 18-37; pg 51, lines 1-25). The specification also discloses that antibodies can be conjugated to a therapeutic agent (pg 51, line 20). However, the specification does not disclose any methods or working examples that indicate labeled anti-108P5H8 antibodies or fragments thereof diagnose a disease or are cytotoxic. Undue experimentation would be required of the skilled artisan to

determine the optimal quantity, duration, and route of administration of a labeled anti-108P5H8 antibody. There is little or no guidance in the specification indicating what specific tissues and cancers are being targeted by the labeled anti-108P5H8 antibody. Although the specification outlines a prophetic example of administration of an anti-108P5H8 antibody (pg 63), this is not adequate guidance, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Such trial and error experimentation is considered undue. Administration of the antibody is unpredictable because the skilled artisan is not able to determine the effect the antibody in the subject. More specifically, the present invention is unpredictable and complex wherein one skilled in the art may not necessarily diagnose or treat a disease by administration of a labeled anti-108P5H8 antibody. Furthermore, relevant literature teaches that problems are often encountered in the effort to use antibodies, including monoclonal antibodies, as clinical reagents. A few of these problems include: the human immune response to foreign antibodies, low affinity or nonoptimal systemic half-life of antibodies, dose and schedule of administration, expression of antigen on normal tissue, and difficulty in producing sufficient quantities of antibody for therapy, among others (Moore, Clin. Chem 35: 1849-1853, 1989 ; Dillman et al., Cancer Invest 19(8): 833-841, 2001, Table 3). Dillman et al. also teaches that if used for a therapeutic application, for example, monoclonal antibodies are tumor-specific and there is always the potential toxicity against normal tissues (Dillman et al., pg 836, col 2, 2nd full paragraph). Dillman et al. indicates that major toxicities associated with immunoconjugates relate to the cytotoxicity of the substance that is attached and the expression of the tumor-associated antigen on normal tissue (pg 837, col 1, 1st full paragraph). Clinical trials of chemotherapy-antibody conjugates have been discontinued because of significant toxicity

resulting from reactions with antigen on normal cells in the gastrointestinal tract and brain (Dillman et al. pg 837, col 1, 1st full paragraph).

Due to the large quantity of experimentation necessary to determine the optimal quantity, duration, and route of administration of a labeled anti-108P5H8 antibody and to diagnose or treat a disease by administration of a labeled anti-108P5H8 antibody, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, and the state of the art which establishes the unpredictability of the effects of monoclonal antibodies *in vivo*, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

11. Claims 4-7, 9-13, and 78-83 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to an antibody or fragment thereof that specifically binds to a protein having at least 90% sequence identity to SEQ ID NO: 2570. The claims also recite that the antibody is a monoclonal antibody and that the monoclonal antibody is recombinantly produced. The claims recite that the antibody or fragment thereof may be labeled with a detectable marker or an agent. The claims recite a non-human transgenic animal that produces an antibody that specifically binds to a protein having at least 90% homology to SEQ ID NO:

2570. The claims recite a hybridoma that produces an antibody that specifically binds to a protein having at least 90% homology to SEQ ID NO: 2570.

The specification of the instant application teaches embodiments of 108P5H8 proteins comprise variant, homolog, or analog polypeptides that have alterations in the amino acid sequence of 108P5H8 (pg 24, lines 31-34). The specification also discloses that embodiments of the invention include a wide variety of art-accepted variants or analogs of 108P5H8 proteins, such as polypeptides having amino acid insertions, deletions, and substitutions (pg 25, lines 22-24).

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. The specification teaches a 108P5H8 polypeptide (SEQ ID NO: 2570). However, the specification does not teach functional or structural characteristics of the polypeptide in the context of a cell or organism. The description of one polypeptide species (SEQ ID NO: 2570) is not adequate written description of an entire genus of functionally equivalent polypeptides which incorporate all variants and

fragments and with at least 90% sequence identity to the 108P5H8 polypeptide consisting of SEQ ID NO: 2570 and the antibodies that bind these fragments and variants.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

With the exception of the sequence referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only an isolated antibody that binds to a protein consisting of the amino acid sequence of SEQ ID NO: 2570, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear

that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 4-7, 9-13, and 78-83 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. The term "specifically binds" in claims 4-7, 9-13, and 78-83 is a relative term which renders the claims indefinite. The term "specifically binds" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear what the claims are meant to encompass, given that neither the art nor the specification provide a clear definition for, or distinction between, "binds" and "specifically binds". Therefore, the metes and bounds of the claimed invention cannot be determined.

12. Regarding claims 4-7, 9-10, 13, and 78-83, the phrase "thereof" renders the claims vague and indefinite because it is unclear whether the antibody, the fragment, or both the antibody and the fragment specifically bind to a protein.

Priority

Applicant's claim for priority under 35 U.S.C. 119(e) is acknowledged. Therefore, the filing date of 15 December 2000 has been used for the purposes of applying the prior art below.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claim 4 is rejected under 35 U.S.C. 102(b) as being anticipated by Murgia et al. (Am J Physiol (Gastrointest Liver Physiol) 40: G1231-G1239, 1999).

Murgia et al. teaches a zinc transporter protein (named Dri 27) that has 91.2% sequence identity to the polypeptide of SEQ ID NO: 2570 of the instant application (see sequence alignment attached to this Office Action as Appendix A; see amino acids 1-428 of SEQ ID NO: 2570 of the instant application and amino acids 1-429 of Murgia et al.). Murgia et al. also discloses that a polyclonal antibody was raised in rabbit against a synthetic 14 amino acid peptide spanning residues 370-383 of the Dri 27 sequence (pg G1232; Figure 2).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 5-7, 9-10, 12-13, 78-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murgia et al. (Am J Physiol (Gastrointest Liver Physiol) 40: G1231-G1239, 1999) as applied to claim 4 above, in view of Hellstrom et al. (U.S. Patent No.5,869,045).

The teachings of Murgia et al. are set forth above. Murgia et al. does not teach that the antibody is a monoclonal antibody or that the monoclonal antibody is recombinantly produced. Murgia et al. also does not disclose that the monoclonal antibody is a single chain antibody or that it is labeled with a detectable marker. Murgia et al. does not teach that an antibody fragment is selected from the group consisting of Fab, F(ab')2, Fv and sFv or that the antibody is humanized or chimeric. Murgia et al. does not disclose that the antibody is labeled with a diagnostic agent or cytotoxic agent. Murgia et al. also does not teach any specific cytotoxic agents, including radioactive isotopes, chemotherapeutic agents, and toxins.

Hellstrom et al. teaches monoclonal antibodies that bind to a cell membrane antigen found on human carcinoma cells (col 7, lines 55-61). Hellstrom et al. discloses that the antibodies may be produced using hybridoma or recombinant techniques (col 15, lines 18-17; col 18, lines 1-21; col 47-49). Hellstrom et al. states that antibody fragments may be single chain (col 27, lines 21-29). Hellstrom et al. teaches that the antibody fragment may include, for example, the Fab', F(ab')2, Fv, or Fab fragments (col 26, lines 41-54). The Hellstrom patent also teaches that antibodies may be chimeric or humanized (col 4, col 16, lines 51-67; col 17, lines 1-21; col 27, lines 31-66; col 58). Antibodies can be labeled with an appropriate imaging

reagent that produces a detectable signal for the detection of tumors *in vivo* (col 42, lines 1-6). Hellstrom et al. disclose that antibodies may be labeled with radioisotopes, such as ^{131}I, ^{111}In, ^{123}I, ^{99m}Tc, ^{32}P, ^{125}I, ^{3}H, and ^{14}C (col 12, lines 66-67 through col 13, lines 1-7; col 42, lines 7-9; col 65, lines 59-67). Hellstrom et al. teaches that antibodies may be linked to a therapeutic drug or toxin (col 42; lines 52-58). The patent indicates that the therapeutic agents include mitomycin C, vincristine, vinblastine, taxol, etoposide, tenoposide, and colchicine, among many others (col 18, lines 22-63). Finally, Hellstrom et al. teaches that antibodies may be conjugated with immunotoxins, including Pseudomonas exotoxin (PE) and PE40 (col 3; col 67-70; the bottom of col 73 through col 80, lines 1-34).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify or further limit the teachings of Murgia et al. of a polyclonal antibody raised against a synthetic 14 amino acid peptide spanning residues 370-383 of the Dri 27 sequence by utilizing the hybridoma and types of antibodies as taught by Hellstrom et al. The person of ordinary skill in the art would have been motivated to make those modifications to enable monoclonal antibodies and chimeric antibodies (including immunoconjugates and recombinant immunotoxins) to react with cell membrane antigens associated with a large variety of carcinomas for diagnostic and treatment purposes. The person of ordinary skill in the art reasonably would have expected success because similar diagnostic and therapeutic antibodies were already being generated and utilized at the time the invention was made. Therefore, the claimed invention as a whole was clearly *prima facie* obvious over the prior art.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

BEB
Art Unit 1647
30 September 2004

Bridget E. Bunner